IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	ROSENBERG ET AL.	DOCKET NO.:	M/42135
SERIAL NO.	10/530,483	CONFIRMATION NO.:	5340
FILED:	SEPTEMBER 28, 2005	GROUP ART UNIT:	1615
FOR:	METHOD FOR PRODUCING SOLID GALENIC FORMULATIONS USING A CROSSLINKED NON-THERMOPLASTIC CARRIER	EXAMINER:	A. SASAN

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL UNDER 37 C.F.R. §41.37

Sir:

This is an appeal from the final rejection of Claims 1 to 22, mailed on December 23, 2009. Claims 1 to 22 are currently pending.

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REAL PARTY IN INTEREST:

To the best of the undersigned's knowledge, the real party in interest is Abbott GmbH & Co. KG, having a place of business at Max-Planck-Ring 2, in 65205 Wiesbaden, Germany.

RELATED APPEALS AND INTERFERENCES:

To the best of the undersigned's knowledge, there are no other prior and pending appeals, interferences or judicial proceedings within the meaning of 37 C.F.R. §41.37(c)(1)(ii).

STATUS OF THE CLAIMS:

Claims 1 to 22 are currently pending and are being appealed. A copy of these claims is found in the attached Claims Appendix. More specifically, the status of the claims is as follows:

-Claim(s) 1 to 22 is(are) pending;

-Claim(s) 1 to 22 is(are) rejected, and is(are) being appealed;

-Claim(s) -*none*- is(are) allowed;

-Claim(s) -*none*- is(are) withdrawn;

-Claim(s) -*none*- is(are) objected to; and

-Claim(s) -*none*- is(are) canceled.

STATUS OF THE AMENDMENTS:

The current version of Claims 1 to 22 was first presented with appellants' request for continued examination filed on December 09, 2008, and was resubmitted on January 09, 2009, in reply to a Notice of Non-Compliant Amendment mailed on December 19, 2008. No amendments to the claims or other parts of the application were filed subsequent to the final Office action of December 23, 2009.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 1 is the sole independent claim currently pending. Claims 2 to 22 are directly depend upon Claim 1. Claims 5, 9 and 20 are rejected separately from Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 and, thus, will be argued separately.

The remaining dependent claims, i.e., Claims 2 to 4, 6 to 8, 10 to 19, 21 and 22, will not be argued separately, and a detailed summary of the embodiments which are addressed in these dependent claims is omitted as unnecessary.[1)]

a) Independent Claim 1:

Claim 1 is drawn to a particular process for producing solid dosage forms, *see* application page 4, lines 3-7. The process comprises the steps of (*see, e.g.*, application page 2, line 31, to page 3, line 11):

1) forming a moldable cohesive composition comprising
   a) 50 to 99.4% by weight of at least one crosslinked non-thermoplastic carrier,[2)]
   b) 0.5 to 30% by weight of at least one adjuvant selected from the group consisting of thermoplastic polymers,[3)] lipids,[4)] sugar alcohols and sugar alcohol derivatives,[5)] and solubilizers,[6)] and
   c) 0.1 to 49.5% by weight of at least one active ingredient,[7)]

   by heating at a temperature at or above the softening point of the adjuvant (b), but at least 70°C,[8)] in a multi-screw extruder,[9)] and subsequently
2) cooling the moldable composition.

Appellants have surprisingly found that it is possible to produce dosage forms of active ingredients which comprise a predominant proportion of the crosslinked non-thermoplastic carrier (a), in the absence of solvents, through a process which is similar to melt extrusion when the particular adjuvants (b) are additionally used, *see* application page 3, lines 31-36.

The melt extrusion procedure for preparing solid dosage forms of active ingredients requires active component compositions in which a thermoplastic polymeric binder is present in a predominant proportion. The thermoplastic binder *inter alia* brings about melting of the composition under

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1) 37 C.F.R. §41.37(v).
2) Application page 4, indicated lines 9 to 18.
3) Application page 4, indicated line 20, to page 5, indicated line 14.
4) Application page 5, indicated lines 20 to 26.
5) Application page 5, indicated lines 16 to 18.
6) Application page 5, indicated line 28, to page 7, indicated line 3.
7) Application page 7, indicated line 23, to page 10, indicated line 11.
8) Application page 10, indicated lines 13 to 21.
9) Application page 11, indicated lines 14 to 20.

the melt extrusion processing conditions, and also brings about the plastic properties of the extrudate. The plastic properties of the extrudate are essential as they allow reproducible dosing and convenient shaping of the moldable extrudate into the desired drug form. Conventional melt extrusion procedures are, e.g., described by ***Klimesch et al.*** and ***Goertz et al.***[10)]

Before this background, it was surprising that the mixture of components (a) through (c) which is employed in appellants' process forms a moldable, cohesive composition under conditions similar to the melt extrusion procedure, especially since the crosslinked, non-thermoplastic carrier which constitutes the predominant proportion of the mixture has no thermoplastic properties, *see* application page 4, lines 9-12. A predominant proportion of the mixture cannot be softened or molten under the processing conditions of melt extrusion. Crosslinked polyvinylpyrrolidone (crosslinked PVP), for example, decomposes at a temperature of 367°C and, due to the crosslinking, the polymer decomposes before a glass transition temperature can be reached.[11)] The predominant proportion of constituents of appellants' composition, thus, does not melt under the processing conditions and also cannot act as a binder or convey cohesiveness to the mixture. Consequently, predominant proportions of appellants' composition are incapable of imparting plastic properties to the extrudate. It was therefore surprising that a mixture comprising predominant proportions of the carrier (a) and considerably lower proportions of the adjuvant (b), together with the active ingredient (c), forms a moldable and cohesive composition, i.e., a composition of doughy or pasty consistency, when the mixture is heated at a temperature at or above the softening point of the adjuvant (b), but at least 70°C, in a multi-screw extruder, *see* application page 10, line 13, to page 11, line 30.

The doughy or pasty consistency of the extrudate which is obtained in step (1) of appellants' process has the advantage that the extrudate can be shaped similar to the extrudates which are obtained in a melt extrusion procedure, e.g., between belts or rolls, similar to the procedure of ***Klimesch et al.***, or by calendering or hot or cold cutting similar to the procedure of ***Goertz et al.***[12)]

Due to the disintegrant properties of the non-thermoplastic carrier, the dosage forms which are obtained in accordance with appellants' process disintegrate rapidly in an aqueous environment such as gastric juice, *see* application page 3, lines 28-31. Appellants' process, thus, is universally

10) Application page 1, indicated lines 9 to 23. EP 358 105 is a European counterpart application of the teaching of ***Klimesch et al.*** (**US 5,073,379**), and EP 240 904 is a European counterpart application of the teaching of ***Goertz et al.*** (**US 4,801,460**).

11) Para. 2 of "3. Results and Discussion" on page 282, lines 3 to 6, of ***Saavedra et al.***

12) Application page 11, indicated line 32, to page 12, indicated line 4. Regarding EP 358 105 and EP 240 904 see No. (10).

applicable to produce dosage forms with rapid release of active ingredients, *see* application page 2, lines 24–29. The process as well as the release properties of resulting dosage forms are illustrated by Examples 1 and 5 to 7.[13] These examples show that mixtures comprising

(1) 68.17% by weight of the carrier (a) and 7% by weight of the adjuvant (b),

(5) 61.17% by weight of the carrier (a) and 17% by weight of the adjuvant (b),

(6) 51.17% by weight of the carrier (a) and 27% by weight of the adjuvant (b),

(7) 61.17% by weight of the carrier (a) and 17% by weight of the adjuvant (b),

formed hot moldable extrudates which hardened after cooling yielding products which disintegrated in water within a few minutes. Example 3 is a comparative example which illustrates a melt extrusion process in which a thermoplastic binder polymer was employed instead of the carrier component (a) used in Example 1, *see* application page 13, lines 10–18. In both cases, a hot moldable composition was obtained. However, while the cooled extrudate obtained in Example 1 disintegrated in water within a few minutes, the cooled extrudate obtained in Example 3 dissolved in water only after several hours.

b) Dependent Claim 5:

Claim 5 is drawn to a variant of the process of Claim 1 in which the sugar alcohols and derivatives thereof which are recited in (b) are selected from the group consisting of sorbitol, xylitol, mannitol, maltitol, isomalt and mixtures thereof, *see* application page 5, lines 16–18.

c) Dependent Claim 9:

Claim 9 is drawn to a variant of the process of Claim 1 in which the cooled composition is comminuted and compressed to the dosage form, *see* application page 12, lines 4–10. Example 2 is illustrative of this embodiment and shows that the dosage form obtained in this manner, like the product obtained in Example 1, disintegrated within a few minutes, *see* application page 12, line 37, to page 13, line 8. Conversely, Example 4 shows that grinding and compressing of the product obtained in accordance with (*comparative*) Example 3 yielded a dosage form which required more than 3 hours to disintegrate, *see* application page 13, lines 20–26.

d) Dependent Claim 20:

Claim 20 is drawn to a variant of the process of Claim 1 which further comprises hot or cold cutting the extrudate to form small-particle granulates, *see* application page 12, lines 2–4.

13) Application page 12, indicated lines 17 to 35, and page 13, indicated line 28, to page 14, indicated line 28.

GROUND(S) OF REJECTION TO BE REVIEWED:

I. Whether the Office action erred asserting that the subject matter of appellants' Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 was *prima facie* obvious under 35 U.S.C. §103 in light of the teaching of ***Klimesch et al.*** **(US 5,073,379)** when taken in view of the disclosure of ***Thacharodi et al.*** **(EP 0 960 620)**.

II. Whether the Office action erred asserting that the subject matter of appellants' Claim 5 was *prima facie* obvious under 35 U.S.C. §103 in light of the teaching of ***Klimesch et al.*** (ibid.) when taken in view of the disclosures of ***Thacharodi et al.*** (ibid.) and ***Endicott et al.*** (US **3,087,860**).

III. Whether the Office action erred asserting that the subject matter of appellants' Claim 9 was *prima facie* obvious under 35 U.S.C. §103 in light of the teaching of ***Klimesch et al.*** (ibid.) when taken in view of the disclosures of ***Thacharodi et al.*** (ibid.) and ***Goertz et al.*** (US **4,801,460**).

IV. Whether the Office action erred asserting that the subject matter of appellants' Claim 20 was *prima facie* obvious under 35 U.S.C. §103 in light of the teaching of ***Klimesch et al.*** (ibid.) when taken in view of the disclosures of ***Thacharodi et al.*** (ibid.) and ***Goertz et al.*** (ibid.).

BRIEF SUMMARY OF THE REFERENCED ART:

a) **Klimesch et al.** (*US 5,073,379*):[14]

The reference describes a continuous process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing an active compound, and shaping the still plastic extrudate, *see* col. 1, lines 5-9. The extrudable pharmaceutical mixtures are mixtures which are pasty due to the melting or softening of one or more components and, in particular, mixtures which contain pharmacologically acceptable, thermoplastic binder polymers, *see* col. 3, lines 1-23. The thermoplastic binder must soften or melt in the total mixture of all components at from 50 to 180°C, *see* col. 3, lines 24-25. Conventional auxiliaries may be included in a total amount of up to 100% by weight, based on the binder polymer, and such auxiliaries include, e.g., extenders, stearic acid or its salts, methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal starch or corn starch, potato starch and polyvinyl alcohol, as well as wetting agents, preservatives, disintegrants, adsorbents, colorants and flavorings, *see* col. 4, lines 30-40. Example 3 illus-

14) The European counterpart application, EP 358 105, is acknowledged/referenced in the application, *see* page 1, indicated line 9 et seq., and page 11, indicated line 32 et seq.

trates a preparation in which crosslinked PVP is employed in as a disintegrant in a composition of (*i*) 47.5 parts of binder polymer, (*ii*) 2.5 parts of the disintegrant; and (*iii*) 50.0 parts of theophylline as active ingredient, *see* col. 6, lines 48–59.

b) Thacharodi et al. (***EP 0 960 620***):

The reference describes a composition for oral administration comprising a substituted pyridyl sulfinyl benzimidazole as active ingredient and a pharmaceutically acceptable carrier. The carrier comprises a polymer having vinyl pyrrolidone monomeric units, such as thermoplastic or crosslinked polyvinylpyrrolidone or a thermoplastic vinyl pyrrolidone–vinyl acetate (NVP–VAc) copolymer which acts as a stabilizing excipient, *see* page 2, lines 5 to 7, and page 4, line 43, to page 5, line 4. The drug–carrier mixture is in form of a simple powder blend which may be converted into granules, and the blend or granules is(are) filled into enteric capsules, *see* page 3, lines 12–15, which renders the preparation of the dosage forms simple, fast and economical, *see* page 3, lines 23–24. Example 6 illustrates the preparation of a powder blend in which crosslinked PVP serves as a diluent and stabilizer, and the conversion thereof into granules. Accordingly,

1) 20 wt.–parts of omeprazole and 100 wt.–parts of Kollidon® CL (*crosslinked PVP*) were mixed to form the powder blend;
2) 20 wt.–parts of Akomed R® and 10 wt.–parts of Gelucire® 33/01 were heated to 60°C for 20 minutes, stirred well and then cooled to 30°C; and
3) 120 wt.–parts of the powder blend obtained in (1) were granulated with 30 wt.–parts of the liquid obtained in (2).

The granulate was screened and filled into capsules, *see* page 7, lines 40–56.

c) Endicott et al. (***US 3,087,860***):

The reference describes a method to prolong the release of a drug from a plastic carrier which involves fusing the individual particles of the plastic carrier in a compressed drug–plastic mixture by a certain vapor treatment, *see* col. 1, lines 10–17. Methods of producing the blend of polymer powder or granulate and drug crystals or granules include *inter alia* milling or mixing and extruding the drug–plastic mixture, *see* col. 4, lines 21–23. The drug–polymer blend is compressed into a foramious body, *see* col. 3, lines 53–63, and vapor treatment with a volatile organic solvent softens the surface of the individual plastic particles allowing them to fuse, *see* col. 2, lines 17–31.

d) Goertz et al. (*US 4,801,460*):[15]

The reference describes a process for the preparation of solid pharmaceutical forms using an N-vinylpyrrolidone polymer as a thermoplastic binder which employs injection molding or melt extrusion and shaping, *see* col. 1, lines 5-8. The thermoplastic binder is required to soften or melt in the total mixture of all components at from 50 to 180°C so that the melt can be extruded, *see* col. 2, lines 25-28. Conventional auxiliaries may be contained in the mixture in a total amount of up to 100% by weight, based on the binder polymer, and such auxiliaries include, e.g., extenders, stearic acid or its salts, methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal starch or corn starch, potato starch and polyvinyl alcohol, as well as wetting agents, preservatives, disintegrants, adsorbents, colorants and flavorings, *see* col. 5, lines 38-48. crosslinked PVP is employed in Example 3 as a disintegrant in a composition comprising (*i*) 47.5 parts of an NVP/VAc copolymer as binder, (*ii*) 2.5 parts of the disintegrant; and (*iii*) 50.0 parts of theophylline as active ingredient, *see* col. 6, lines 30-42.

ARGUMENT(S)

In rejecting claims under 35 U.S.C. §103, it is incumbent upon the first instance to establish a factual basis to support the legal conclusion of obviousness.[16] In so doing, the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966) must be made which *inter alia* includes a determination of the scope and the content of the prior art. In determining the scope and content of the prior art, the references have to be considered as a whole, have to be viewed from the vantage point of one having ordinary skill at the pertinent time, and have to be considered without the benefit of impermissible hindsight vision afforded by the claimed invention.[17] A conclusion of obviousness also requires that one of ordinary skill would have had, at the pertinent time, "a reasonable expectation" that making the asserted combination would have resulted in the patented claim.[18] The analysis under Section 103 need not seek out precise teachings directed to the specific subject matter of the challenged claim because a Court can take account of the inferences and creative steps that a person of ordinary skill in the art would

15) The European counterpart application, EP 240 904, is acknowledged/referenced in the application, *see* page 1, indicated line 9 et seq., and page 11, indicated line 32 et seq.

16) See *In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988).

17) W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

18) *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir.1986).

employ. E.g., "*When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.*"[19] However, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness.[20]

The rejections of appellants' claims are based on error in ascertaining the scope and the content of the prior art from the vantage point of one of ordinary skill at the pertinent time. Upon proper appreciation of the referenced art, there was no reasonable expectation that combining the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims would have resulted in a moldable, cohesive composition and, thus, in an extrudate which can be shaped and processed similar to the extrudates obtained in a melt extrusion process. Consequently, the reasons for rejecting appellants' claims lack the the factual basis or rational underpinning which is necessary to support a finding of obviousness.

I. The assertion that the subject matter of appellants' Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 was prima facie *obvious under 35 U.S.C. §103 in light of the teaching of* **Klimesch et al.** *when taken in view of the disclosure of* **Thacharodi et al.** *is, for the following reasons, deemed to be in error.*

The rejection acknowledges that ***Klimesch et al.*** fail to teach a process in which the melt-extruded composition comprises a predominant proportion of a crosslinked, non-thermoplastic carrier, *see* page 4, lines 19-20, and attempts to bridge the gap between the primary reference and appellants' claims asserting that it would have been obvious to one of ordinary skill to employ the non-thermoplastic carrier in the respective amounts because ***Thacharodi et al.*** show a stable composition comprising a high level of crosslinked PVP, *see* page 5, line 14, to page 6, line 4.

Thacharodi et al. describe stable compositions which comprise high levels of carrier polymer, i.e., thermoplastic PVP and/or NVP-VAc and/or crosslinked PVP, *see, e.g.*, examples page 5, line 50, to page 7, line 56. The rejection disregards, however, that the respective compositions are in form of powders or granules, *see, e.g.*, page 3, lines 12-15, and examples. The reference also illustrates in Example 6 a composition which comprises (a) 66.67% by weight of crosslinked

19) *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007), emphasis added.

20) *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

PVP, (b) 13.3% by weight of Akomed R® (*a fatty acid glyceride*), and 13.3% by weight of the active ingredient omeprazole, *see* page 7, lines 40-56. However, the compositions addressed in the secondary reference are in powder or granular form, and the powders or granules are employed as such. The secondary reference, thus, is not concerned with providing cohesive, pasty blends of the constituents which are necessary for the success of the melt extrusion process of ***Klimesch et al.***, *see* col. 3, lines 1-6. In fact, the secondary reference not only fails to address or suggest cohesive blends of the respective constituents but also points out that the preparations obtained using the powders or granules are advantageous *inter alia* because conversion of a powder blend into core units such as granules, pellets or tablets is not required, *see* page 3, lines 16-24.

The rejection fails to appreciate that the compositions of ***Thacharodi et al.*** are in powder or granular form whereas it is necessary in the melt extrusion process of ***Klimesch et al.*** to obtain a pasty, moldable extrudate, *see* col. 3, lines 1-6. The rejection also disregards that ***Klimesch et al.*** specifically provide that conventional auxiliaries may *only* be present in the melt extrusion composition in a total amount of up to 100% by weight, based on the amount of the thermoplastic binder, *i.e.*, the amount of thermoplastic binder is equal to or larger than that of all auxiliaries, *see* col. 4, lines 30-40. It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.[21] Neither the teaching of ***Klimesch et al.*** nor the disclosure of ***Thacharodi et al.*** reasonably suggests or fairly implies that it is possible to convert any mixture which comprises from 50 to 99.4% by weight of a non-thermoplastic carrier (a), and at most 30% by weight of an adjuvant (b), into a moldable cohesive composition. In fact, the limitations placed on the amounts of auxiliaries which are taught by ***Klimesch et al.***, the non-thermoplastic properties of the carrier (a), and the fact that the compositions of ***Thacharodi et al.*** are in powder or granular form rather than of pasty, cohesive consistency, are deemed to leave the impression that the mixtures of ***Thacharodi et al.***, or mixtures having a similarly high content of non-thermoplastic carrier, would not be suited for the purposes of ***Klimesch et al.***'s process. A reference teaches away if it leaves the impression that the product would not have the property sought by the applicant.[22]

The rejection argues, "*Combining prior art elements according to known methods to yield predictable results would have been obvious to one of ordinary skill in the art*[,]" and asserts that it was "*apparent that one of ordinary skill in the art would have had a reasonable expectation of*

21) *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965).

22) *In re Caldwell*, 319 F.2d 254, 256 (CCPA1963).

success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, ..." *see* page 6, lines 4–11; emphasis added, *see* also page 13, lines 12–15. However, "producing the claimed invention" includes *forming a moldable cohesive composition* of the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims. On the basis of the referenced art, one of ordinary skill could not reasonably expect that processing the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims would yield an extrudate which is in form of a moldable cohesive composition and which, thus, can be shaped similar to extrudates obtained in a melt extrusion process. To the contrary, in light of the express teaching of ***Klimesch et al.*** that conventional auxiliaries may *only* be present in the melt extrusion composition in a total amount of up to 100% by weight, based on the amount of the thermoplastic binder, the non-thermoplastic properties of the carrier (a), and the fact that the compositions addressed by ***Thacharodi et al.*** are in form of powders or granules, and are not designed for forming moldable cohesive compositions, one of ordinary skill could not reasonably expect to arrive at a moldable cohesive composition. Therefore, the pertinent consistency of the extrudate is deemed to be an unexpected result, and the reasonable expectation of success is deemed to be absent.

Further, the rejection argues, "*One of ordinary skill in the art would know that the amount of diluents in pharmaceutical formulations comprising active ingredients is in quantity sufficient amounts [sic] and can be modified based on the desired functionality of the diluent. Therefore, since the crosslinked PVP functions as a disintegrant/stabilizer/diluent, one of ordinary skill in the art would find it obvious to modify the level based on the desired function, i.e., high level for diluent and fast disintegration, low level for slower disintegration[,]*" *see* page 13, lines 4–12. The approach is by far too general to be reasonably applicable in the context of the melt extrusion technology employed in the process of ***Klimesch et al.***, or to reasonably reflect the vantage point of one having ordinary skill in the art involving melt extrusion at the time appellants made the invention. Again, moldability of the extrudate is a prerequisite of the melt extrusion process described by ***Klimesch et al.***, and an extrudate which lacks the cohesive and moldable consistency would render the composition unsuited for the purposes of the process of ***Klimesch et al.*** However, if a proposed modification would render the prior art invention which is being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modi-

fication.[23] The motivation to increase the amount of crosslinked PVP in the mixture of ***Klimesch et al.*** is lacking, independent of the desired function of the auxiliary, be it the extender/diluent properties, the stabilizing properties regarding pyridyl sulfinyl benzimidazoles addressed in ***Thacharodi et al.***, or the disintegrant properties of crosslinked PVP.

Diluting or extending properties are *inter alia* provided in the mixtures of ***Klimesch et al.*** by the binder polymer. Thus, the active ingredient can be diluted in the melt-extrudable preparation by increasing the relative amount of the binder. Such a modification would not bear the risk of losing the pasty properties of the extrudate and the risk of rendering the process of ***Klimesch et al.*** unsatisfactory. The stabilizing effects on pyridyl sulfinyl benzimidazoles addressed by ***Thacharodi et al.*** are obtained by any polymer which comprises vinylpyrrolidone monomer units, *see* page 4, line 29 et seq. Suitable polymers include thermoplastic vinylpyrrolidone polymers and one having ordinary skill will readily appreciate that the stabilizing effects can be realized by employing a thermoplastic binder polymer, rather than a non-thermoplastic alternative, without risking to render the process of ***Klimesch et al.*** unsatisfactory. The non-thermoplastic properties of crosslinked PVP, together with the teaching of ***Klimesch et al.*** deter from increasing the amount of the disintegrant at the cost of the amount of binder beyond the at most 1:1 weight ratio as a loss in binding effectivity of the thermoplastic polymer would render the extrudate granular and, thus, unsuitable for the purposes of the melt extrusion process of ***Klimesch et al.*** Also, one of ordinary skill will appreciate that conventional pharmaceutical preparations generally comprise disintegrants in amounts of, e.g., 2 to 20% by weight.[24] The amounts in which disintegrants are generally incorporated into conventional pharmaceutical preparations, therefore, also could not direct one of ordinary skill in the pertinent technology to increase the amount of disintegrant relative to the amount of the binder in the mixture of ***Klimesch et al.*** to a weight ratio beyond the at most 1:1 ratio which is taught by ***Klimesch et al.*** The conclusion that, "*since the crosslinked PVP functions as a disintegrant/stabilizer/diluent, one of ordinary skill in the art would find it obvious to modify the level based on the desired function, i.e., high level for diluent and fast disintegration, low level for slower disintegration*" is, therefore, deemed to lack the rational underpinning necessary to support a conclusion of obviousness where the process involves *forming a moldable cohesive composition* from a mixture comprising from 50 to 99%-wt. of a crosslinked non-thermoplastic carrier and from 0.5 to 30%-wt. of a particular adjuvant.

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23) MPEP §2143.01 (V), Rev. 6, Sept. 2007, page 2100-140, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

24) Col. 3, indicated lines 27 to 39, at indicated lines 34 to 36, of ***US 6,485,745***; of record.

At least for the foregoing reasons, neither the teaching of ***Klimesch et al.*** when taken alone, nor the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** provides for an apparent reason to combine the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims, and there was no reasonable expectation that doing so would result in a moldable, cohesive composition and, thus, in an extrudate which can be shaped and processed similar to the extrudates obtained in a melt extrusion process.

II. *The assertion that the subject matter of appellants' Claim 5 was* prima facie *obvious under 35 U.S.C. §103 in light of the teaching of* **Klimesch et al.** *when taken in view of the disclosures of* **Thacharodi et al.** *and of* **Endicott et al.** *is, for the following reasons, deemed to be in error.*

Claim 5 depends upon Claim 1 and incorporates the pertinent elements thereof by reference. To the extent that the rejection relies upon the teaching of ***Klimesch et al.*** and the disclosure of ***Thacharodi et al.*** as allegedly showing the elements of Claim 1, *see* page 13, line 21, appellants respectfully refer to the foregoing arguments.

With a particular view to the additional reference, the rejection notes, "*Endicott teaches adjuvants such as sorbitol and mannitol (Col. 3, lines 67-70) and teaches that a drug-plastic combination can be mixed and extruded (Col. 4, lines 21 -23)*[,]" *see* page 4, lines 1-3. The rejection purports, "*It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by Klimesch, ...*" *see* page 14, lines 4-7, emphasis added, and that "*One of ordinary skill in the art would have done this because sugar alcohols such as sorbitol and mannitol are known in the art to be used as excipients or adjuvants and can be included in extrudable compositions, as evidenced by the teaching of Endicott[,]*" *see* page 4, lines 13-15.

Endicott et al. are silent as to the consistency of drug-plastic extrudates. The procedure of ***Endicott et al.*** involves compressing a *particulate composition* which *inter alia* comprises a drug-plastic mixture and subsequently fusing the individual plastic particles by vapor treatment with a volatile organic solvent which softens the surface of the plastic particles, *see* col. 2, lines 17-31. The consistency of an extrudate which is obtained when mixing and extruding the drug-plastic combination, therefore, is of no concern for the purposes of ***Endicott et al.***'s process. In principle, any particulate solid matter can be extruded including, *e.g.*, sand. However, the expression "extrusion," per se, does not suggest or imply that the process involves a polymer melt even if a polymer

is present, and/or that the extrudate which is obtained in an extrusion is in form of a moldable, cohesive composition. Thus, a person of ordinary skill would not reasonably consider the extrusion of a drug-plastic combination as addressed by ***Endicott et al.*** and the melt extrusion of ***Klimesch et al.*** to be equivalent processes. Correspondingly, a person having ordinary skill in the art would not reasonably consider the compositions of ***Endicott et al.*** *per se* suitable for the purposes of ***Klimesch et al.***'s melt extrusion process.

When contemplating the teaching of ***Klimesch et al.*** together with the disclosure of ***Endicott et al.***, one of ordinary skill may consider the water-soluble components of the secondary reference, *see* col. 3, lines 64-70, to fall within the realm of conventional pharmaceutical auxiliaries which may be present in the melt-extrudable compositions of the primary reference in a total amount of up to 100% by weight, based on the binder polymer, *see* col. 4, lines 30-40. Thus, ***Endicott et al.*** at best provide that sorbitol and mannitol may be incorporated into the mixture of ***Klimesch et al.*** as conventional pharmaceutical auxiliaries. However, a person of ordinary skill in the art who contemplated the teaching of ***Klimesch et al.*** in view of the disclosure of ***Endicott et al.***, would not have been motivated to reduce the amount of binder polymer relative to the total amount of pharmaceutical auxiliaries in general, and in particular relative to the amount of cross-linked, non-thermoplastic carriers.

At least for the foregoing reasons, neither the teaching of ***Klimesch et al.*** when taken alone, nor the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and/or ***Endicott et al.*** provides for an apparent reason to combine the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims, and there was no reasonable expectation that doing so would result in a moldable, cohesive composition and, thus, in an extrudate which can be shaped and processed similar to the extrudates obtained in a melt extrusion process.

III. The assertion that the subject matter of appellants' Claim 9 was prima facie *obvious under 35 U.S.C. §103 in light of the teaching of* **Klimesch et al.** *when taken in view of the disclosures of* **Thacharodi et al.** *and of* **Goertz et al.** *is, for the following reasons, deemed to be in error.*

Claim 9 depends upon Claim 1 and incorporates the pertinent elements thereof by reference. To the extent that the rejection relies upon the teaching of ***Klimesch et al.*** and the disclosure of ***Thacharodi et al.*** as allegedly showing the elements of Claim 1, *see* page 15, line 19, appellants respectfully refer to the foregoing arguments.

With a particular view to the additional reference, the rejection notes, "*Goertz teaches ... 'Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hot-face cutting to give granules or molding to give tablets . . . cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets' (Col. 5, lines 11 -20)[,]" see* page 16, lines 1-9.

The process of ***Goertz et al.*** is similar to the process of ***Klimesch et al.*** in that solid pharmaceutical forms are prepared by mixing an active ingredient with a polymeric binder at an elevated temperature, *e.g.*, in an extruder to obtain a plastic, moldable composition which may be shaped or injection molded. Also similar to ***Klimesch et al.***, ***Goertz et al.*** note that conventional auxiliaries, including extenders (*diluents*) and disintegrating agents (*i.e., crosslinked PVP*), may be incorporated in a total amount of up to 100% by weight, based on the binder polymer, *see* col. 5, lines 38-48. As is the case in the process of ***Klimesch et al.***, the success of the process of ***Goertz et al.*** depends upon forming a still plastic, pasty and thus moldable extrudate. The disclosure of the additional secondary reference, thus, further emphasizes the limitations placed on the amounts of auxiliaries which may be incorporated into a melt-extrudable composition as employed in the process of ***Klimesch et al.*** As such, the disclosure of ***Goertz et al.*** cannot direct a person of ordinary skill to a process which involves *forming a moldable cohesive composition* comprising the pertinent ingredients in the respective amounts set forth in Claim 1 and incorporated into Claims 9 by reference. At best, ***Goertz et al.*** merely provide that a cohesive, plastic extrudate as is obtained in the melt extrusion process of ***Klimesch et al.*** may be injection molded, or may be hot- or cold-cut into granules which, in turn, may be compressed to give tablets. The disclosure of ***Goertz et al.***, taken together with the teaching of ***Klimesch et al.*** and the disclosure of ***Thacharodi et al.*** would not have suggested to one having ordinary skill to reduce the amount of binder polymer relative to the total amount of pharmaceutical auxiliaries in general, and in particular relative to the amount of cross-linked, non-thermoplastic carriers.

At least for the foregoing reasons, neither the teaching of ***Klimesch et al.*** when taken alone, nor the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.*** and/or ***Goertz et al.*** provides for an apparent reason to combine the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims, and there was no reasonable expectation that doing so would result in a moldable, cohesive composition and, thus, in an extrudate which can be shaped and processed similar to the extrudates obtained in a melt extrusion process.

IV. The assertion that the subject matter of appellants' Claim 20 was prima facie *obvious under 35 U.S.C. §103 in light of the teaching of* **Klimesch et al.** *when taken in view of the disclosures of* **Thacharodi et al.** *and of* **Goertz et al.** *is, for the following reasons, deemed to be in error.*

Claim 20 depends upon Claim 1 and incorporates the pertinent elements thereof by reference. To the extent that the rejection relies upon the teaching of ***Klimesch et al.*** and the disclosure of ***Thacharodi et al.*** as allegedly showing the elements of Claim 1, *see* page 15, line 19, appellants respectfully refer to the foregoing arguments.

With a particular view to the additional reference, the rejection notes, *"Goertz teaches ... 'Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hot-face cutting to give granules or molding to give tablets ... cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets' (Col. 5, lines 11 -20)[,]" see* page 16, lines 1-9.

The arguments in No. (III.) regarding the subject matter of Claim 9 apply *mutatis mutandis*. Both ***Goertz et al.*** and ***Klimesch et al.*** limit the amount in which conventional auxiliaries, including extenders (*diluents*) and disintegrating agents (*i.e., crosslinked PVP*), may be incorporated into the mixtures to a total amount of 100% by weight, based on the binder polymer, *see* col. 5, lines 38-48. The success of the process of ***Klimesch et al.*** as well as that of ***Goertz et al.*** depends upon obtaining a still plastic, pasty and thus moldable extrudate. The disclosure of the additional secondary reference, thus, further emphasizes the limitations placed on the amounts of auxiliaries which may be incorporated into a melt-extrudable composition. The disclosure of ***Goertz et al.***, therefore, cannot direct a person of ordinary skill to a process which involves *forming a moldable cohesive composition* comprising the pertinent ingredients in the respective amounts set forth in Claim 1 and incorporated into Claims 20 by reference. At best, ***Goertz et al.*** merely provide that a cohesive, plastic extrudate as is obtained in the melt extrusion process of ***Klimesch et al.*** may be injection molded, or the moldable extrudate may be hot- or cold-cut into granules which, in turn, may be compressed to give tablets. The disclosure of ***Goertz et al.***, taken together with the teaching of ***Klimesch et al.*** and the disclosure of ***Thacharodi et al.***, however, would not have suggested to one having ordinary skill to reduce the amount of binder polymer relative to the total amount of pharmaceutical auxiliaries in general, and in particular relative to the amount of cross-linked, non-thermoplastic carriers.

At least for the foregoing reasons, neither the teaching of ***Klimesch et al.*** when taken alone, nor the teaching of ***Klimesch et al.*** when taken in view of the disclosure of ***Thacharodi et al.***

and/or *Goertz et al.* provides for an apparent reason to combine the constituents (a) to (c) in the requisite amounts and in the manner set forth in appellants' claims, and there was no reasonable expectation that doing so would result in a moldable, cohesive composition and, thus, in an extrudate which can be shaped and processed similar to the extrudates obtained in a melt extrusion process.

CONCLUSION

In light of the foregoing arguments as well as the explanations already presented by appellants in their papers of January 09, 2009, August 12, 2009, and March 16, 2010,[25] appellants respectfully urge that the final rejections were in error. It is respectfully requested that the rejections be reversed. Favorable action is solicited.

The fee set forth in 37 C.F.R. §41.20(b)(2) in the amount of *$540.00* is paid herewith by credit card. Further, the Commissioner is herewith authorized to charge any additional fees under 37 C.F.R. §1.16 or §1.17 that may be required in connection with this paper, or credit any overpayment, to Deposit Account No. 14.1437. Please reference Attorney Docket No.: M/42135.

Respectfully submitted,

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25) The respective papers are herewith incorporated by reference.

CLAIMS APPENDIX:

THE CLAIMS INVOLVED IN THE APPEAL:

1. A process for producing solid dosage forms, comprising

forming a moldable cohesive composition which comprises

a) 50 to 99.4% by weight of at least one crosslinked nonthermoplastic carrier,

b) 0.5 to 30% by weight of at least one adjuvant selected from the group consisting of thermoplastic polymers, lipids, sugar alcohols, sugar alcohol derivatives and solubilizers and

c) 0.1 to 49.5% by weight of at least one active ingredient,

by heating at a temperature at or above the softening point of the adjuvant, but at least 70°C, in a multi-screw extruder and subsequently cooling the moldable composition.

2. The process according to claim 1, where the composition comprises

a) 50 to 90% by weight of at least one crosslinked nonthermoplastic carrier,

b1) 5 to 30% by weight of at least one thermoplastic polymer,

b2) 0.5 to 20% by weight of at least one solubilizer,

c) 0.1 to 45.5% by weight of at least one active ingredient.

3. The process according to claim 1, where the crosslinked nonthermoplastic carrier is selected from the group consisting of crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcellulose and mixtures thereof.

4. The process according to claim 1, where the thermoplastic polymer is a homo- or copolymer of vinylpyrrolidone.

5. The process according to claim 1, where the sugar alcohol is selected from the group consisting of sorbitol, xylitol, mannitol, maltitol, the sugar alcohol derivative isomalt and mixtures thereof.

6. The process according to claim 1, where the lipid is selected from the group consisting of fatty acids, fatty alcohols, fats, waxes, mono- and diglycerides, phosphatides and mixtures thereof.

7. The process according to claim 1, where the solubilizer is selected from the group consisting of sorbitan fatty acid esters,

polyalkoxylated fatty acid esters, polyalkoxylated ethers of fatty alcohols and mixtures thereof.

8. The process according to claim 1, where the active ingredient has a solubility in water at 25ºC of less than 1 mg/ml.

9. The process according to claim 1, where the cooled composition is comminuted and compressed to the dosage form.

10. The process according to claim 9, wherein at least one tableting aid is employed, and wherein the at least one tableting aid is selected from the group consisting of colloidal silica, calcium hydrogen phosphate, lactose, microcrystalline cellulose, starch, and magnesium stearate.

11. The process according to claim 1, wherein components a) - c) are mixed before heating.

12. The process according to claim 1, wherein components a) - c) are mixed during heating.

13. The process according to claim 1, wherein components a) - c) are mixed after heating at least one of the components.

14. The process according to claim 1, wherein the moldable cohesive composition is homogenized to distribute the active ingredient.

15. The process according to claim 1, further comprising melting the at least one adjuvant in the presence of the nonthermoplastic carrier, and admixing the active ingredient, wherein the steps of melting and admixing are carried out prior to the step of forming the moldable cohesive composition.

16. The process according to claim 1, wherein the composition remains in the multi-screw extruder for a residence time of less than 5 minutes.

17. The process according to claim 1, wherein the composition remains in the multi-screw extruder for a residence time of less than 3 minutes.

18. The process according to claim 1, further comprising shaping the moldable cohesive composition between at least one belt and at least one roll.

19. The process according to claim 1, further comprising shaping the moldable cohesive composition by calendaring in a calendar with two molding rolls.

20. The process according to claim 1, further comprising extruding the moldable composition, and hot or cold cutting to form small-particle granules.

21. The process according to claim 1, wherein the temperature is from 70°C - 180°C.

22. The process according to claim 1, wherein the process is carried out in the absence of a solvent.

EVIDENCE APPENDIX:

1. *Saavedra et al.*, J. Phys. IV France 125, 281–283 (2004)
   The reference was filed with appellants' paper of August 12, 2009, in reply to a non-final Office action mailed on April 13, 2009. Entry and consideration of the reference is inferred from the statements in No. 1 on page 2 of the subsequent final Office action mailed on December 23, 2009.

2. *Wagner et al.* (US 6,485,745)
   The reference was filed with appellants' paper of March 16, 2010, in reply to the final Office action mailed on December 23, 2009. Entry and consideration of the reference is inferred from the advisory Office action mailed on April 06, 2010, in which No. 8 of the form PTOL-303 was unchecked, and the statements in No. 11 indicate that appellants' paper of March 16, 2010 had been fully considered.

RELATED PROCEEDINGS APPENDIX:

DECISIONS RENDERED BY A COURT OR THE BOARD:

NONE

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Photoacoustic evaluation of molecular weight and crosslinking effects on thermal diffusivity in Poly(N-vinyl-2-pirrolidone)

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Abstract. The thermal diffusivity of Poly(N-vinyl-2-pirrolidone) (PVP) samples was investigated using open photoacoustic cell technique (OPC) as function of molecular weight and crosslinking. Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and X ray diffraction (XRD) techniques were also used to the PVP characterization.

1. INTRODUCTION

Poly(N-vinyl-2-pirrolidone) (PVP) is one of the most frequently investigated linear vinyl polymers for its medical and biological applications [1]. PVP is a white and hygroscopic powder, which has been used in a very large number of applications due to its remarkable properties (amphiphylic character, complexing ability, biocompatibility, etc). According to the structural formula, the monomer unit have an amphiphilic character because it contains a highly polar amide group conferring hydrophilic and polar-attracting properties, and also apolar methylene and methine groups in the backbone and the ring, conferring hydrophobic properties [2]. In contrast with most of polymers, it is readily soluble both in water and in a large number of organic solvents. On the other hand, this polymer is insoluble in common esters, ethers, hydrocarbons and ketones.

The thermal diffusivity is an important physical parameter that is strongly dependent on the compositional and structural variables of the polymeric material. In this note, we report thermal properties of the PVP as function of molecular weight and crosslinking. We used the open photoacoustic cell (OPC) technique to measure the effective thermal diffusivity (α_{eff}) of PVP as function of molecular weight and crosslinking. It is well known that the photoacoustic methods had been successfully applied to the thermal characterization of polymers [3–6]. The characterization of thermophysical properties of the PVP was also performed by using Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA) and X ray Diffraction analysis (XRD).

2. EXPERIMENTAL

PVP powder samples with different weight average molecular weights $\bar{M}_w$ (24.000, 40.000, 55.000, 1.300.000 $\left[\frac{g}{mol}\right]$) and crosslinking were obtained from Aldrich™. Disk-plate like samples were made by pressing PVP powders (~ 470 $[MPa]$). The effective thermal diffusivity (α_{eff}) measurement setup considers the well known OPC technique. The mechanically modulated light from 100 $[mW]$ Ar ion laser is focused onto the sample. The sample was mounted on top of a commercial electret microphone

and sealed with vacuum grease. To ensure optical opacity of the samples, a thin Al foil was glued with thermal paste to the illuminated surface. The PA signal from the microphone was lock-in amplified and its amplitude and phase were digitally recorded as function of the modulation frequency f. The α_{eff} was obtained by fitting PA amplitude signals in the thermally thick regime, i.e. for ranges of f where $l_s \gg \mu_s$, with l_s thickness and $\mu_s = \sqrt{\frac{\alpha_{eff}}{\pi f}}$ the thermal diffusion length of the sample [6, 7].

The TGA and DSC analysis were done in PVP powder samples, using a simultaneous thermal analyser TGA/DSC Polymer Laboratories STA 625. Samples ($2 - 3$ $[mg]$) were placed inside aluminium pans and heated under flowing nitrogen ($41\left[\frac{mL}{min}\right]$) ranging from 25 to 550 [°C], at $10\left[\frac{°C}{min}\right]$. So, the corresponding thermograms and thermal decomposition profiles were obtained, which are characteristic descriptions of each polymer. In addition, the cristallinity degree (%) of PVP samples was calculated from XRD analysis. The X-ray diffractograms were performed with a Siemens D500 diffractometer with Cu K_α line.

3. RESULTS AND DISCUSSION

The figure 1 shows the measured properties of PVP samples as function of $\bar{M}_w$. It can be seen small values of α_{eff} at small $\bar{M}_w$ values. After that there is a rise in the α_{eff} as the $\bar{M}_w$ become larger. On the other hand, PA measurements of α_{eff} display the same $\bar{M}_w$ dependence when compared with T_g values obtained from DSC. This can be interpreted in terms of specific heat becuase small α_{eff} value could mean large specific heat values. While heating samples the internal energy of the system increases and this energy can be used in other molecular events such as internal conformational transitions. The detectable conformational changes occur at the T_g, where the polymer has gained enough internal energy to rotate $C - C$ bonds in the macromolecule backbone. For low $\bar{M}_w$ this changes are allowed at lower T which is reflected on a decreasing T_g.

As the crosslinked PVP can not be expressed in terms of $\bar{M}_w$, its properties are shown in the table 1. The T_g value for crosslinked PVP is not observed. In fact, the crosslinking phenomena work against the conformational transitions, so then T_g increases. When crosslinks are large enough the required motions to reach the glass temperature regime can never be achieved and the polymer will degrade before reaching T_g [8]. The measured decomposition temperature was 367 °C, so T_g for crosslinked PVP could be higher than this value. This observation also agrees with an expected high α_{eff} value, as we discussed above. However, the relative increase of α_{eff} can be associated to the porosity of compact PVP samples too. Scanning electron microscopy (SEM) shows polymeric matrix containing domains of air inclusions within the compacts [Fig. 2]. The α_{eff} depends on both PVP and enclosed air. It had been described that the thermal diffusivity of air-filled porous material is modified with porosity [7, 9, 10], since the room temperature air thermal diffusivity is relatively high, $\alpha_{air} = 21\left[\frac{mm^2}{s}\right]$. Regardless the porosity constant effect on PVP compact samples, we can qualitatively consider the observed α_{eff} dependence on $\bar{M}_w$ for this kind of porous samples. In conclusion, the inspected properties of PVP are a function of composition and structure as well as $\bar{M}_w$ and crosslinking.

Acknowledgements

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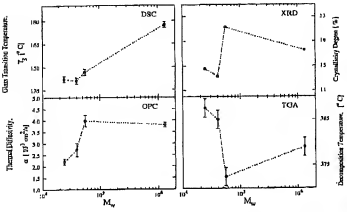

Figure 1. Thermal and Physical properties of PVP as function of molecular weight $\bar{M}_w$: Effective thermal diffusivity α_{eff} (left bottom), Glass transition temperature T_g (left top), Decomposition temperature (right bottom) and Cristallinity degree (right top)

Figure 2. SEM image of PVP crosslinked.

Table 1. Measured Properties of PVP crosslinked

Effective Thermal Diffusivity	$8.64 \pm 2.51 \left[\frac{mm^2}{s}\right]$
Decomposition Temperature	$367\,°C \pm 5°C$
Cristallinty Degree	13.9 %

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